

5 represented by P101Q; (8) a valine amino acid residue  
mutated to another Group 2 amino acid residue at position  
111, in one embodiment the mutation represented by V111I;  
(9) a Group 4 amino acid residue mutated to a Group 2  
amino acid residue at position 133, in one embodiment the  
10 mutation represented by S133L; (10) a Group 3 amino acid  
residue mutated to a Group 2 amino acid residue at  
position 141, in one embodiment the mutation represented  
by E141V; (11) a Group 3 amino acid residue mutated to a  
Group 5 amino acid residue at position 141, in one  
15 embodiment the mutation represented by E141K; (12) a Group  
4 amino acid residue mutated to Group 6 amino acid residue  
at position 153, in one embodiment the mutation  
represented by C153Y; (13) a Group 4 amino acid residue  
mutated to a Group 5 amino acid residue at position 153,  
20 in one embodiment the mutation represented by C153R; (14)  
a Group 4 amino acid residue mutated to a Group 1 amino  
acid residue at position 281, in one embodiment the  
mutation represented by T281A; (15) a Group 3 amino acid  
residue mutated to a Group 2 amino acid residue at  
25 position 367, in one embodiment the mutation represented  
by N367I; (16) a Group 3 amino acid residue mutated to a  
Group 6 amino acid residue at position 367, in one  
embodiment the mutation represented by N367Y; (17) a Group  
1 amino acid residue mutated to Group 4 amino acid residue  
30 at position 389, in one embodiment the mutation  
represented by P389S; and (18) a Group 1 amino acid  
residue mutated to a Group 2 amino acid residue at  
position 389, in one embodiment the mutation represented  
by P389L.

35 In some embodiments of the first aspect, the  
invention provides regulator proteins with at least two,  
or at least three, or at least four, or at least five, or  
at least six, or at least seven, or at least eight, or at  
least nine, or at least ten, or at least eleven, or at  
40 least twelve, or at least thirteen, or at least fourteen,  
or at least fifteen, or at least sixteen, or at least  
seventeen, or at least eighteen of the above described  
specific mutations.

5 In other embodiments of the first aspect, the invention provides an isolated lovE variant regulator protein selected from the group consisting of SEQ ID NO:41, SEQ ID NO:42, SEQ ID NO:43, SEQ ID NO:44, SEQ ID NO:45, SEQ ID NO:46, SEQ ID NO:47, SEQ ID NO:48, SEQ ID NO:49, SEQ ID NO:50, SEQ ID NO:51, SEQ ID NO:52, SEQ ID NO:53, SEQ ID NO:54, SEQ ID NO:55, SEQ ID NO:56, SEQ ID NO:57, SEQ ID NO:58, SEQ ID NO:59, SEQ ID NO:60, SEQ ID NO:61, SEQ ID NO:62, SEQ ID NO:63, SEQ ID NO:64, and SEQ ID NO:65.

15 In a second aspect, the invention provides a nucleic acid molecule encoding a lovE regulator of the first aspect of the invention. By way of non-limiting example, the invention provides a nucleic acid molecule encoding the lovE variant regulator protein selected from the group consisting of SEQ ID NO:66, SEQ ID NO:67, SEQ ID NO:68, SEQ ID NO:69, SEQ ID NO:70, SEQ ID NO:71, SEQ ID NO:72, SEQ ID NO:73, SEQ ID NO:74, SEQ ID NO:75, SEQ ID NO:76, SEQ ID NO:78, SEQ ID NO:79, SEQ ID NO:81, SEQ ID NO:82, SEQ ID NO:83, SEQ ID NO:84, SEQ ID NO:86, SEQ ID NO:87, SEQ ID NO:88, SEQ ID NO:89, and SEQ ID NO:90.

25 In a third aspect, the invention provides a method of increasing the activity of a protein that regulates secondary metabolite production comprising: (a) selecting a nucleic acid comprising a polynucleotide encoding a protein regulator of secondary metabolite production; (b) mutating the nucleic acid to create a plurality of nucleic acid molecules encoding variant regulator proteins of secondary metabolite production; and (c) selecting a variant regulator protein with more activity than the cognate, wild-type protein.

35 In various embodiments of the third aspect, the secondary metabolite is a fungal secondary metabolite. In certain embodiments of the third aspect, the protein regulator of secondary metabolite production is a transcription factor. In certain embodiments of the third aspect, the protein regulator of secondary metabolite production is a transmembrane transporter, protein that

5 mediates secretion, kinase, G-protein, cell surface  
receptor, GTPase activating protein, guanine nucleotide  
exchange factor, phosphatase, protease, phosphodiesterase,  
bacterial protein toxin, importin, RNA-binding protein,  
SCF complex component, adherin, or protein encoded within  
10 a biosynthetic cluster. In certain other embodiments of  
the third aspect, the variant regulator protein is  
selected to have more activity in a heterologous cell  
and/or more activity in a homologous cell than the  
cognate, wild-type regulator protein. In certain  
15 embodiments, the variant regulator protein is selected to  
have more activity in a heterologous cell and/or more  
activity in a homologous cell than the cognate, wild-type  
protein and to cause more secondary metabolite to be  
produced in a homologous cell and/or a heterologous cell  
20 when compared to the cognate, wild-type regulator protein.  
In a particularly preferred embodiment, the variant  
regulator protein is a lovE variant regulator protein.

In a fourth aspect, the invention provides a method  
of increasing production of a secondary metabolite  
25 comprising: (a) selecting a nucleic acid comprising a  
polynucleotide encoding a protein regulator of secondary  
metabolite production; (b) mutating the nucleic acid to  
create a plurality of nucleic acid molecules encoding  
variant regulator proteins of secondary metabolite  
30 production; (c) selecting a variant regulator protein with  
more activity than the cognate, wild-type protein; and (d)  
expressing the selected variant regulator protein in a  
cell, thereby increasing production of the secondary  
metabolite in the cell.

35 In various embodiments of the fourth aspect, the  
secondary metabolite is a fungal secondary metabolite. In  
certain embodiments of the third aspect, the protein  
regulator of secondary metabolite production is a  
transcription factor. In certain embodiments of the  
40 fourth aspect, the protein regulator of secondary  
metabolite production is a transmembrane transporter, a